DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-301/S-015

The R.W. Johnson Pharmaceutical Research Institute
Attention: William R. Sisco
Associate Director, Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Sisco:

Please refer to your supplemental new drug application dated September 29, 2000, received October 2, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO-CEPT® (desogestrel/ethinyl estradiol).

We acknowledge receipt of your submission dated February 20, 2001.

This "Changes Being Effected" supplemental new drug application provides for the following labeling changes that were requested in the Supplement Request Letter dated June 6, 2000:

Physician Package Insert:

CLINICAL PHARMACOLOGY

The second paragraph under Pharmacodynamics was revised from:

> "Receptor binding studies, as well as studies in animals and humans, have shown that 3-keto-desogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity."

To:

> "Receptor binding studies, as well as studies in animals, have shown that 3-keto-desogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity. The relevance of this latter finding in humans in unknown.

WARNINGS

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Thromboembolism (*Note the change in order for this subcategory*).

The following changes were made to the first and second paragraphs:

> "An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Data from case-control and cohort studies report that oral contraceptives containing desogestrel (OTRHO-CEPT contains desogestrel) are associated with a two-fold increase in the risk of venous thromboembolic disease as compared to other low-dose (containing less than 50 mcg of estrogen) pills containing other progestins. According to these studies, this two-fold risk increases the yearly occurrence of venous thromboembloic disease by about 10-15 cases per 100,000 women.
>
> Earlier case control studies on older formulations have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease is not related to the length of use and disappears after pill use is stopped."

To:

> "An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped."

The Division requested the addition of the following sentences at the end of the above revised paragraph:

> "Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk."

Instead, revised wording for these requested sentences was submitted in the FPL:

> "Several epidemiologic studies indicate that third generation oral contraceptives~~, including those~~ containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per

10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk."

WARNINGS

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

b. Myocardial Infarction (*Note the change in order for this subcategory*)

The following text was deleted in this subsection after the sentence; "Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.":

~~"Desogestrel has minimal androgenic activity (see CLINICAL PHARMACOLOGY) and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestagen has minimal androgenic activity than when the activity is greater (100)."~~

Detailed Patient Package Insert:

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risks of developing blood clots.

The following sentence was revised from:

"These risks are greater with desogestrel-containing oral contraceptives, such as ORTHO-CEPT®, than with other low-dose pills."

To:

"The risks of these side effects may be greater with desogestrel-containing oral contraceptives such as ORTHO-CEPT® than with certain other low-dose pills."

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

Please revise the following sentences to the original requested wording for labeling consistency and accuracy among desogestrel containing oral contraceptive products:

WARNINGS

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Thromboembolism

"……Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk."

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted February 20, 2001, patient package insert submitted September 29, 2001). These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-301/S-015." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research